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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/419,817
Filing Date	October 18, 1999
First Named Inventor	Xiaohua HUANG et al
Group Art Unit	1634
Examiner Name	B. Forman
Total Number of Pages in This Submission	
Attorney Docket Number	03848.80923

ENCLOSURES *(check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) ____
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)* in triplicate
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) *(please identify below)*:

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Michelle L. Holmes-Son, Reg. No. 47,660
Signature	Michelle L. Holmes-Son
Date	September 26, 2002

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PTO/SB/17 (10-01)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 320

Complete if Known	
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METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 19-0733

Deposit Account Name: Banner & Witcoff, Ltd.

The Commissioner is authorized to: *(check all that apply)*
☒ Charge fee(s) indicated below ☒ Credit any overpayments
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below	=	Fee Paid
Total Claims		- ** =	0	X		=	0
Independent Claims		- ** =	0	X		=	0
Multiple Dependent				X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	320
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17 (q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 320

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Michelle L. Holmes-Son	*Registration No. Attorney/Agent)*	47,660	*Telephone*	(202) 508-9100
Signature				*Date*	September 26, 2002

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PATENT

#23 appeal Brief

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Xiaohua Huang *et al.*	)	Group Art Unit: 1634
	)	
Serial No. 09/419,817	)	Examiner: B. J. Forman
	)	
Filed: October 18, 1999	)	Atty. Dkt. No. 003848.80923

For: **IDENTIFICATION OF ALLELES**

BRIEF ON APPEAL

Michelle Holmes-Son
Reg. No. 47,660
BANNER & WITCOFF, LTD.
1001 G Street N.W.
Washington, D.C. 20001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Xiaohua Huang *et al.*	)	Group Art Unit: 1634
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Serial No. 09/419,817	)	Examiner: B. J. Forman
	)	
Filed: October 18, 1999	)	Atty. Dkt. No. 003848.80923

For: **IDENTIFICATION OF ALLELES**

BRIEF ON APPEAL

Assistant Director for Patents
Washington, D.C. 20231

Sir:

An original and two copies of this brief are submitted. Please charge the $320.00 fee for filing the brief to our Deposit Account No. 19-0733. Appellants filed the Notice of Appeal on July 26, 2002. If any additional fee is required, please charge our Deposit Account No. 19-0733.

REAL PARTIES IN INTEREST

The real party in interest in this application is Affymetrix, to which this application is assigned.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 17-22 are canceled. Claims 1-16 and 23-38 stand rejected. Claims 1-16 and 23-38 are appealed.

STATUS OF AMENDMENTS

No amendment after final rejection has been filed. The appealed claims are shown in Appendix I.

SUMMARY OF THE INVENTION

The invention is drawn to a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample. (Page 2, lines 13-22; Figure 1.) A region of DNA comprising a polymorphic locus in a sample is amplified with a primer pair to form amplified DNA products. A first primer of the pair terminates at its 3' end at the polymorphic locus. The first primer also comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA. Upon amplification a first strand and a second strand of DNA are formed. The first strand comprises a 5' portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe. The amplified DNA products are labeled to form labeled amplified DNA products. The labeled, amplified DNA products are hybridized to the probe on the solid support such that the second strand hybridizes to the probe on the solid support.

ISSUE

The prima facie case of obviousness must fail because Vary and Lane, considered as a whole, do not suggest the claimed methods.

GROUPING OF CLAIMS

Claims 1-16, and 23-38 stand or fall together with respect to the issue.

ARGUMENT

The prima facie case of obviousness must fail because Vary and Lane, considered as a whole, do not suggest the claimed methods.

Section 103 (a) of Title 35 of the United States Code states that for claims to be patentable, they must be non-obvious over the prior art:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Rijckaert* 9 F.3d 1531, 1532 (Fed. Cir. 1993) citing *In re Oetiker* 977 F.2d 1443, 1445 (Fed. Cir. 1992). The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142.

To determine whether there is some suggestion or motivation to combine or modify reference teachings, both the invention and the references must be considered as a whole. "35 U.S.C. § 103 requires that obviousness be determined with respect to the invention as a whole." *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1143 (Fed. Cir. 1985). "When determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *Ecolochem, Inc v. Southern California Edison Co.* 227 F.3d 1361, 1372 citing *In re Beattie*, 974 F.2d 1309, 1311-1312, *quoting Lindemann*, 730 F.2d 1462 (Fed. Cir. 2000). Once the invention and the prior art references have been considered as a whole, the desirability of selecting specific teachings from the references to combine must be met by the identification of some suggestion, teaching, or motivation in the prior art that would have taught a person of ordinary skill in the field of the invention to make the combination. *In re Dance* 160 F.3d 1339, 1343 citing *In re Fine* 837 F.2d 1074, 1075 (Fed. Cir. 1998). To not identify such motivation is to use the claimed invention as an instruction manual, or template, to piece together the teachings of the prior art, which is impermissible. *In re Fritch* 972 F.2d 1260, 1266 citing *In re Gorman* 933 F.2d 982, 987 (Fed. Cir. 1992).

The factual inquiries of *Graham v. John Deere Co.* provide the structural framework with which to evaluate the teachings of the invention and the prior art as a whole and thus patentability under 35 U.S.C. § 103(a):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

383 U.S. 1, 17 (1966).

The scope and content of the prior art.

The first factual inquiry under *Graham* is to determine the scope and content of the prior art. *Id.* The U.S. Patent and Trademark Office asserts four combinations of prior art against claims 1-16 and 23-38 under 35 U.S.C. § 103(a). Each rejection cites Vary *et al.*, U.S. Patent No. 4,851,331 ("Vary"), and Lane *et al.*, U.S. Patent No. 6,165,714 ("Lane") as primary and secondary references. Tertiary references are cited in rejections of different sets of dependent claims.

Claims 1 2, 4, 5, 7-9, 11-14, 16, 23, 24, 26, 27, 29-31, 33-36, and 38 are rejected over Vary in view of Lane. Claims 3, 10, 25, and 32 are rejected over Vary in view of Lane, Hames *et al.*, *Nucleic Acid Hybridization: a practical approach*, 1988, pages 35, 36, and 42-44; ("Lane")), and Lapidus *et al.*, U.S. Patent No. 5,670,325 ("Lapidus"). Claims 6 and 28 are rejected over Vary in view of Lane and Mullan, U.S. Patent No. 5,455,169 ("Mullan"). Claims 15 and 37 are rejected over Vary in view of Lane and Lockhart *et al.*, U.S. Patent No. 5,556,752 ("Lockhart"). The scope and content of each prior art reference is described below.

Primary reference

Vary, "Method and kit for polynucleotide assay including primer-dependent DNA polymerase," U.S. Patent No. 4,851,331.

Figure 3A and 3B of Vary visually depict the method used in the rejection and are reproduced below.

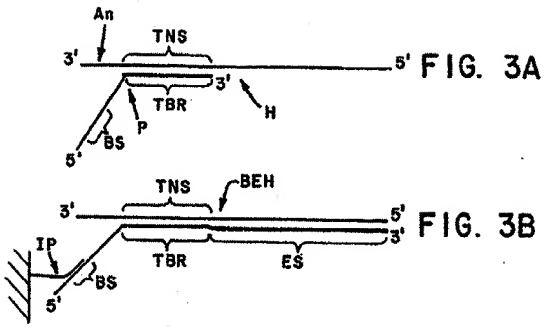


FIG. 3A

FIG. 3B

Vary teaches a method of detecting a target nucleotide sequence in a nucleic acid sample. (Column 2, lines 31-33.) An oligonucleotide (P) comprising a 3' portion (TBR) complementary to the target nucleotide sequence (TNS) is hybridized to the target nucleic acid (An). (Figure 3A; Column 2, lines 49-52.) The oligonucleotide may also contain a 3' terminal nucleotide that detects a polymorphic locus in the target nucleic acid. (Column 12, lines 19-30.) The oligonucleotide is extended using a polymerase and nucleoside triphosphates to form an extended oligonucleotide (ES) hybridized to the target nucleic acid (An). (Figure 3B; Column 3, lines 10-16.) The nucleoside triphosphates may be labeled. (Column 3, lines 54-63.) The labeled, extended, oligonucleotide hybridized to the target DNA is detected. (Column 4, lines 53-56.)

In a specific embodiment of Vary the labeled, extended, oligonucleotide is separated from the unincorporated, labeled, nucleoside triphosphates of the reaction mixture before the step of detection. (Column 4, lines 14-16.) In this embodiment, the oligonucleotide comprises a 5' portion (BS) that is complementary to a probe (IP) on a solid support. (Figure 3B; Column 7, lines 46-49.) The labeled, extended, oligonucleotide can be directly hybridized to a probe on the solid support via the 5' portion of the oligonucleotide. (Column 7, lines 43-49.) The unbound reagents used in the reaction mixture can then be separated from the bound, extended,

oligonucleotide before detection. (Column 7, lines 52-56.)

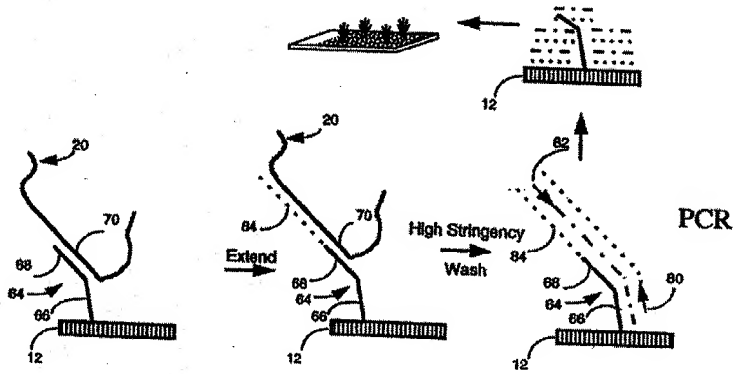
Vary does not teach or suggest a primer that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support." Vary also does not teach or suggest amplification of the target nucleotides with a pair of primers.

Secondary reference

Lane, "Devices and methods for detecting nucleic acid analytes in samples," U.S. Patent No. 6,165,714.

Figure 9B of Lane visually depicts the specific embodiment of the method and is reproduced below.

Fig. 9B



Lane teaches methods for detecting a target nucleotide sequence in a nucleic acid sample. (Column 1, lines 31-33.) A nucleic acid sample is applied to an array of probes on a solid support (12). The probes (64) comprise a 3' sequence (68) that is complementary to the target nucleotide sequence (70). The probes hybridize to the target nucleotide sequence via the 3' sequence. A diffusion-limiting matrix is applied to the solid support. The target nucleotide sequence hybridized to the probe is amplified. The amplification products form localized foci on the solid support (represented as bushes in top center panel) because the diffusion-limiting matrix prevents the diffusion of the amplification products from the site where the target nucleic acid hybridized to the probe. The foci are detected. (Column 3, lines 48-65.)

In a specific embodiment of the invention Lane teaches that the probe (64) hybridized to the target nucleotide sequence (70) is extended (84) in a single strand extension reaction. (Figure 9B; Column 8, lines 29-31.) A pair of primers (80 & 82), one of which is identical to a portion of the probe (80), is used to amplify the extended probe (64 & 84). (Figure 9B; Column 8, lines 37-38.) The amplification products form diffusion-limited foci (represented as bushes in top center panel) which are then detected. (Figure 9B; Column 8, line 41.)

Lane does not teach or suggest an amplification primer that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support." Specifically, Lane's primer is only identical to the probe. Lane also does not teach hybridization of amplification products to a probe on a solid support.

Tertiary References

Each of the following references were cited in combination with Vary and Lane to teach a limitation recited in a dependent claim.

1. Hames, "Nucleic Acid Hybridization: a practical approach," 1988, pages 35, 36, and 42-44.

Hames teaches protocols for labeling nucleic acids. The protocols teach how to end-label DNA fragments with terminal deoxynucleotidyl transferase (pages 35-36) and how to label nucleic acids without using radioactivity (pages 42-44).

Hames does not teach or suggest a primer that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support." Hames also does not teach or suggest amplification.

2. Lapidus, "Method for the detection of clonal populations of transformed cells in a genomically heterogeneous cellular sample," U.S. Patent No. 5,670, 325.

Lapidus teaches a method of detecting a trace amount of mutated DNA derived from cancer or precancer cells in a biological sample. (Column 3, lines 13-16.) The mutated DNA is detected by hybridizing labeled probes to the mutated DNA (column 12, lines 19-25, column 12, lines 59-62; column 19, lines 19-28), or by extending oligonucleotides on sample nucleic acids in

single-strand extension reactions (column 16, line 37 to column 17, line 38). The probes or oligonucleotides are complementary to the target DNA. (Column 16, lines 37-40.)

Lapidus does not teach or suggest an oligonucleotide that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support." Lapidus also does not teach or suggest amplification of target nucleotides. Lapidus only teaches single strand extension.

3. Mullan, "Nucleic acids for diagnosing and modeling Alzheimer's disease," U.S. Patent No. 5,455,169.

Mullan teaches that mutations at codons 670 and 671 of the amyloid precursor protein 770 can be used to detect, treat, and screen subjects for Alzheimer's disease. (Column 3, lines 16-19.) The mutations can be detected by methods that include "polymerase chain reaction (PCR) methodology, restriction length polymorphism (RFLP) analysis, and single strand conformational analysis (SSCA)." (Column 8, lines 20-23.) The primers used to perform PCR or the oligonucleotide used to perform SSCA are complementary to the nucleotide sequence of the amyloid precursor protein 770. (Column 10, lines 28-33.)

Mullan does not teach or suggest an oligonucleotide that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support."

4. Lockhart, "Surface-bound, unimolecular, double-stranded DNA," U.S. Patent No. 5,556,752.

Lockhart teaches high-density oligonucleotide arrays and methods of using such high-density oligonucleotide arrays. (Column 2, lines 31-53.) Probes are attached to the arrays. The

probes can be double-stranded oligonucleotides that are used to identify cellular proteins that bind to the double-stranded probe sequences. (Column 6, lines 61-65.) The probes can also be single-stranded oligonucleotides that identify a complementary target nucleotide sequence. (Column 18, lines 49-51.)

Lockhart does not teach or suggest an oligonucleotide that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support."

Differences between the prior art and claims 1-16 and 23-38

The second factual inquiry under *Graham* is to ascertain the differences between the prior art and the claims at issue. 383 U.S. at 17. Independent claim 23 is discussed here as representative of the claims at issue. Claim 23 is directed to a method to prepare samples for analysis to determine a nucleotide at a polymorphic locus in a nucleic acid sample. A region of DNA comprising a polymorphic locus is amplified with a primer pair to form amplified DNA products. A first primer of the pair terminates at its 3' end at the polymorphic locus. The first primer also comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA. The amplification reaction forms a first strand and a second strand of DNA. The first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe. The amplified DNA products are labeled to form labeled amplified DNA products. The labeled, amplified DNA products are hybridized to the probe on the solid support such that the second strand hybridizes to the probe on the solid support.

Neither the primary reference (Vary) or the secondary reference (Lane) used in each of the rejections teaches an amplification primer that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support" as recited in the rejected claims. Vary teaches an oligonucleotide that is extended on a target nucleotide sequence and that can hybridize to a probe on a solid support. The oligonucleotide can comprise a 3' terminal nucleotide that can detect a single base pair polymorphic locus. The oligonucleotide also comprises a 5' end complementary to a probe on a solid support and a 3' portion that is complementary to the target nucleotide sequence. Lane teaches an amplification primer that has a 5' portion that is identical to a probe attached to a solid support but which does not terminate at its 3' end at a polymorphic locus or have a 3' portion complementary to the target nucleic acid sequence.

The tertiary references (Hames, Lapidus, Mullan, and Lockhart) also do not teach a primer that "terminates at its 3' end at a polymorphic locus" and "comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support." Each of these references teaches that an oligonucleotide can be used as a probe, a primer, or in a single strand extension reaction. The oligonucleotide taught by each reference is fully complementary to the target nucleic acid across its full length.

The primary reference (Vary) also does not teach or suggest amplification as recited in the rejected claims. Vary teaches extending an oligonucleotide hybridized to target nucleic acids yielding the same amount of product (or less) as the amount of the target nucleic acid. Lane teaches amplification but does not teach hybridization of amplification products to a probe on a

solid support.

Level of skill in the art

The third factual inquiry under *Graham v. John Deere Co.* is to resolve the level of skill in the pertinent art. 383 U.S. at 17. The person of ordinary skill is described in *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*:

> The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such factors may be present in every case, and one or more of them may predominate.

807 F.2d 955,962-63, 1 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 1986).

The person of ordinary skill would have been aware of all pertinent prior art relating to methods of detecting target nucleotides in a sample of nucleic acids. Nonetheless, the person of ordinary skill, having read each of the cited references, would not have discerned any reason or motivation in any of the references to combine teachings in the way required to achieve the present invention.

Determination of Nonobviousness Against the Background of the Graham Factors

The person of ordinary skill would not have modified Vary's method with Lane's method because, upon considering the references as a whole as instructed in *Ecolochem, Inc v. Southern California Edison Co.*, the person of ordinary skill would conclude that Vary's and Lane's methods are completely different. Thus one of ordinary skill in the art would not have looked to Lane for teachings with which to modify Vary.

First, Vary and Lane detect different products formed in different media. Vary detects a single-strand extension product. Lane detects an amplification product. Vary's product was formed in solution and Lane's product was formed tethered to a solid support.

Second, Vary and Lane teach different associations of the labeled, detected, target nucleic acids with the solid support. Vary associates the single strand extension product via hybridization to a probe on the solid support. Lane associates the amplification products to the solid support via a diffusion-limiting matrix.

Third, Vary and Lane perform their method steps in a completely different order. Vary teaches that first an *oligonucleotide is hybridized* to the target nucleic acid, then the *oligonucleotide is extended* on the target and finally the *extended oligonucleotide is hybridized to a probe* on a solid support. Lane teaches that first the *target nucleotide is hybridized to a probe* on a solid support, then the *probe is extended* on the target nucleotide, and finally amplification *primers are hybridized* to the extended target nucleotide.

Fourth, the function of the solid support in each of the referenced methods is different. Vary uses the solid support to separate the labeled, single strand, extension product from unincorporated labeled nucleoside triphosphates in the reaction mixture. (Column 4, lines 13-21.) Lane uses the solid support as a substrate on which the target nucleotides are amplified and identified.

Thus the methods taught by Vary and Lane are so distinct that their combination would not suggest itself to the person of ordinary skill in the art. Moreover, nothing in Vary or Lane suggests the desirability of combining their teachings. The tertiary references also do not provide the required motivation to combine. Since none of the prior art references provide a

specific teaching, suggestion, or motivation to combine specific, selected elements of Vary's method with specific, selected elements of Lane's method, it appears that the Patent Office has used appellants' own disclosure as a template in forming the rejection. This amounts to hindsight reconstruction which is impermissible. *Texas Instruments Inc. v. U.S. ITC* 988 F.2d 1165, 1178 (Fed. Cir. 1993).

The Patent Office has failed to apply the proper standard required to establish motivation to modify or combine reference teachings. To meet the standard the Patent Office must identify some suggestion, teaching, or motivation in the prior art that would have taught a person of ordinary skill in the field of the invention to make the combination. *In re Dance* 160 F.3d 1339, 1343 citing *In re Fine* 837 F.2d 1074, 1075 (Fed. Cir. 1998). The Patent Office has selectively chosen specific isolated teachings from Vary and Lane to combine. However, no suggestion, teaching, or motivation has been identified in either Vary or Lane that would have suggested the desirability of making those combinations.

The Patent Office asserts that one of ordinary skill in the art would have been motivated combine these specific teachings to detect the coding strand of the target DNA duplex. (Advisory Action, page 2, lines 8-9.)

> [W]hile the coding and non-coding strands of the target DNA contain the same amount of information, the information (i.e. sequence) is not the same. Because the information is different, the skilled practitioner in the art would have been motivated to detect the presence of the polymorphism in the coding strand because the coding strand determines function. Additionally, because the information (i.e. sequence) is different, one of skill in the art having a probe which detects the sequence of the polymorphism in the coding strand would have been motivated to detect the coding strand...because their coding strand-specific probe would not detect the polymorphism in the non-coding strand.

Advisory Action at page 2, lines 11-19.

To achieve the desired result asserted by the Patent Office, *i.e.*, to "detect the presence of the polymorphism in the coding strand," it would not have been necessary to modify Vary's extendible oligonucleotide with Lane's amplification primer. Even if Vary's method extends and detects the non-coding strand, the polymorphism in the coding strand would be indirectly determined. Determining the sequence of one strand of double-stranded DNA automatically determines the sequence of the opposite strand of DNA due to complementarity of base pairing between the strands. An A on one strand implies a T on the opposite strand. Thus there would have been no need to modify Vary's method to determine a polymorphism in a coding strand as alleged by the Patent Office. The equivalence of the two strands for detecting polymorphisms is supported by cited tertiary reference Lapidus, U.S. Patent No. 5,670,325.

> Double-stranded DNA in the sample is converted to single-stranded DNA. Then, either the coding strand or the anti-coding strand for both alleles is isolated from the sample. As will be evident from the following discussion, methods disclosed herein are indifferent as to whether coding strand or anti-coding strand is retained in the sample.
>
> An oligonucleotide probe is constructed that is complementary to a portion of the region of the single-base polymorphism, said portion ending at the nucleotide that is immediately 3' to the polymorphic nucleotide, regardless of whether the 5'-3' (coding) stand or the 3'-5' (anticoding) strand is used as a template.

Column 16, lines 31-42. As in Lapidus, Vary's detection of polymorphisms is indifferent as to whether the coding or anti-coding strand is determined. Thus the alleged motivation provided by the Patent Office for modifying Vary's teaching must fail.

The Patent Office also asserts that one of ordinary skill in the art would have been motivated to combine the specific teachings of Vary and Lane to arrive at the claimed method to

increase sensitivity. The Patent Office alleges that one of ordinary skill in the art would have been motivated to make the specific combination because,

> Lane specifically teaches that their localized amplification increases analyte-detection sensitivity (Column 3, lines 48-65, Column 5, lines 24-45 and Column 6, lines 26-41.) Therefore, one skilled in the art would have been motivated to apply the primers and amplification of Lane to the method of Vary for the expected benefits of increased polymorphism-detection sensitivity as suggested by Lane thereby increasing the sensitivity of the Vary method.

Advisory Action at page 3, lines 3-8. Lane however, does not teach that amplification *per se* increases target nucleic acid detection sensitivity. Lane teaches that the formation of distinct foci of amplification products in the diffusion-limiting matrix on the solid support increases target nucleic acid detection sensitivity.

> The invention provides several advantages. For example, the diffusion path of an analyte that is required for it to be detected using the devices of the invention is 'straight down.' That is, the analyte can contact the solid support and form a 'productive' complex (see, e.g., FIG. 1A) at any place on the surface of the solid support; lateral diffusion is not required. In contrast, other array-type assays known in the art employ discrete loci (e.g., spots, squares, etc.) for detecting different analytes on a single device.

Column 5, lines 26-34. This teaching would not lead one to select amplification separately from the other aspects of Lane's method.

CONCLUSION

For the reasons given above, the rejection of claims 1-16 and 23-38 under 35 U.S.C. § 103 (a) is improper. The Board of Patent Appeals and Interferences should reverse the rejection.

Respectfully submitted,

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APPENDIX I. APPEALED CLAIMS

1. A method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, comprising the steps of:

amplifying a region of DNA comprising a polymorphic locus in the sample to form amplified DNA products using a primer pair, wherein a first primer of the pair terminates at its 3' end at the polymorphic locus, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA, to form a first strand and a second strand, wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe;

labeling the amplified DNA products to form labeled amplified DNA products;

hybridizing the labeled, amplified DNA products to the probe on the solid support such that the second strand hybridizes to the probe on the solid support; and

detecting labeled, amplified DNA products hybridized to the probe on the solid support, wherein the presence of said labeled amplified DNA products on the solid support indicates that the nucleic acid sample contains at the polymorphic locus a nucleotide which is the same as the 3' terminal nucleotide of the primer.

2. The method of claim 1 wherein the step of labeling couples a labeled nucleotide to a 3' end.

3. The method of claim 1 wherein terminal transferase catalyzes the step of labeling.

4. The method of claim 1 wherein the nucleotide is fluorescently labeled.

5. The method of claim 1 wherein the nucleotide is radioactively labeled.

6. The method of claim 1 wherein the nucleotide is enzymatically labeled.

7. The method of claim 1 wherein the nucleotide is epitopically labeled.

8. The method of claim 4 further comprising the step of:

optically detecting fluorescent label on the solid support.

9. The method of claim 8 wherein two primer pairs are employed, wherein the first primer of each of the first and second pairs of primers terminate at their 3' ends in distinct nucleotides, and wherein each 5' portion of each of said first primers is identical in sequence to all or part of a distinct probe at a known location on the solid support.

10. The method of claim 8 wherein quantities of fluorescent label at known locations on the solid support are compared, wherein the known locations represent different allelic forms of the polymorphic locus having different nucleotides at the polymorphic locus, thereby determining a ratio of nucleotides at the polymorphic locus in the sample.

11. The method of claim 10 wherein the ratio of nucleotides at two or more polymorphic loci are determined simultaneously.

12. The method of claim 1 wherein the sample comprises DNA from two or more individuals.

13. The method of claim 1 wherein two or more regions of DNA, each of which comprises a

polymorphic locus, are amplified in a single reaction mixture.

14. The method of claim 1 wherein the solid support is beads.

15. The method of claim 1 wherein the solid support is a microtiter dish.

16. The method of claim 1 wherein the solid support is a high density array.

23. A method to prepare samples for analysis to determine a nucleotide at a polymorphic locus in a nucleic acid sample, comparing the steps of

amplifying a region of DNA comprising a polymorphic locus in the sample to form amplified DNA products using a primer pair, wherein a first primer of the pair terminates at its 3' end at the polymorphic locus, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA to form a first strand comprising a portion identical to all or part of the probe and a second strand which comprises a 5' portion complementary to all or part of the probe;

labeling the amplified DNA products to form labeled amplified DNA products; and

hybridizing the labeled, amplified DNA products to the probe on the solid support such that the second strand hybridizes to the probe on the solid support, thereby forming prepared samples for analysis.

24. The method of claim 23 wherein the step of labeling couples a labeled nucleotide to a 3' end.

25. The method of claim 23 wherein terminal transferase catalyzes the step of labeling.

26. The method of claim 23 wherein the nucleotide is fluorescently labeled.

27. The method of claim 23 wherein the nucleotide is radioactively labeled.

28. The method of claim 23 wherein the nucleotide is enzymatically labeled.

29. The method of claim 23 wherein the nucleotide is epitopically labeled.

30. The method of claim 26 further comprising the step of:

optically detecting fluorescent label on the solid support.

31. The method of claim 30 wherein two primer pairs are employed, wherein the first primer of each of the first and second pairs of primers terminate at their 3' ends in distinct nucleotides, and wherein each 5' portion of each of said first primers is identical in sequence to all or part of a distinct probe at a known location on the solid support.

32. The method of claim 30 wherein quantities of fluorescent label at known locations on the solid support are compared, wherein the known locations represent different allelic forms of the polymorphic locus having different nucleotides at the polymorphic locus, thereby determining a ratio of nucleotides at the polymorphic locus in the sample.

33. The method of claim 32 wherein the ratio of nucleotides at two or more polymorphic loci are determined simultaneously.

34. The method of claim 23 wherein the sample comprises DNA from two or more individuals.

35. The method of claim 23 wherein two or more regions of DNA, each of which comprises a

polymorphic locus, are amplified in a single reaction mixture.

36. The method of claim 23 wherein the solid support is beads.

37. The method of claim 23 wherein the solid support is a microtiter dish.

38. The method of claim 23 wherein the solid support is a high density array.